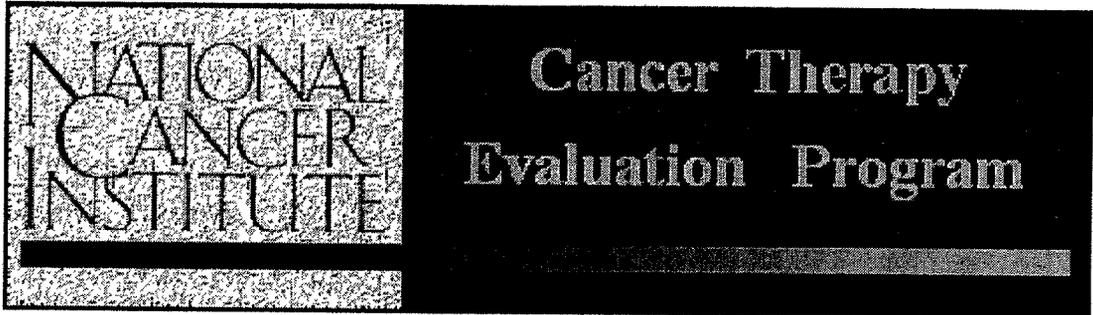


c



COMMON TOXICITY CRITERIA MANUAL

Common Toxicity Criteria, Version 2.0

June 1, 1999

NCI CTEP Help Desk -
Telephone: (301) 840-8202
Fax: (301) 948-2242
E-mail: ncictephelp@ctep.nci.nih.gov

Table of Contents

COMMON TOXICITY CRITERIA QUICK REFERENCE	1
1 INTRODUCTION.....	5
1.1 Purpose of this Manual.....	5
1.2 Making the Entire CTC Available to those Responsible for Grading Adverse Events	5
1.3 Defining Adverse Event	5
1.4 Specificity of the CTC	6
2 ORGANIZATION OF THE CTC.....	6
2.1 Adverse Event Categories in the Revised CTC	6
2.2 Adverse Event Listings	7
2.3 Grades of Adverse Events.....	7
2.4 Adverse Events Not Included in the CTC.....	8
2.5 Where to Find Adverse Events from the 1982 Version of the CTC	8
2.6 Highlights of Important Changes	9
2.7 Appendices to the CTC	10
3 HOW TO GRADE ADVERSE EVENTS	11
3.1 What Not to Grade	11
3.2 Attribution of Causality.....	11
3.3 Grading at Baseline	12
3.4 Documenting Related Adverse Events.....	12
3.5 Grading Adverse Events	17
3.6 Syndromes.....	18
3.7 Dose-limiting Adverse Event.....	18
4 SUPPLEMENTARY FORMS	19
4.1 Adverse Event Module.....	19
4.2 Infection Module.....	19
5 GRADING TOXICITIES IN SPECIAL POPULATIONS.....	19
5.1 Leukemia Special Adverse Event Criteria	19
5.2 Bone Marrow/Stem Cell Transplant	20
5.3 Pediatric Adverse Event Criteria.....	20
6 RADIATION THERAPY TOXICITIES	21
6.1 Acute Radiation Adverse Event.....	21
6.2 Late Radiation Effects.....	22
7 MULTIMODALITY THERAPIES	23
7.1 Grading Adverse Events in Multimodality Therapies when Options are Available ..	23
8 HARMONIZATION WITH THE INTERNATIONAL MEDICAL TERMINOLOGY	23
9 CTC USER TOOLS.....	24
Appendix I: REVISION OF THE COMMON TOXICITY CRITERIA	25
COMMON TOXICITY CRITERIA QUICK REFERENCE GUIDE	

COMMON TOXICITY CRITERIA QUICK REFERENCE

Definition of Adverse Event

- **Toxicity** – Toxicity is NOT clearly defined by regulatory organizations. Toxicity has been described as an adverse event that has an attribution (the relationship to investigational agent) of possible, probable or definite. To minimize confusion, the NCI would recommend that the term toxicity NOT be utilized.

Note: The Cancer Therapy Evaluation Program, Common Toxicity Criteria, Version 2.0 (CTC, v2.0) uses the term “toxicity” for historical reasons, but recommends that the term “adverse event” with its attribution be used instead whenever possible.

- **Adverse Event** – Any unfavorable symptom, sign, or disease (including an abnormal laboratory finding) temporally associated with the use of a medical treatment or procedure that may or may NOT be considered related to the medical treatment or procedure.
- **Common Toxicity Criteria (CTC)**¹ – The CTC, v2.0 provides descriptive terminology for adverse event reporting. A grading (severity) scale is provided for each adverse event term.

Common Toxicity Criteria (CTC) Categories

- CTC, v2.0 contains 24 categories.
- CTC, v2.0 is organized by pathophysiology and anatomy.
- Alphabetical listings of adverse events are placed within categories.
- The entire CTC, v2.0 should always be available for grading adverse events; however, NCI only requires grading of adverse events that occur.

Changes to the CTC, v2.0

Major changes in the new version of the CTC, v2.0 are outlined in Sections 2.4 and 2.5 of this manual.

¹ All studies reviewed and approved after March 5, 1998 must utilize the CTC version 2.0 standards 1998 for adverse event grading and attribution.

Grades (General Definitions)

- 0 = No adverse event or within normal limits
- 1 = Mild adverse event
- 2 = Moderate adverse event
- 3 = Severe and undesirable adverse event
- 4 = Life-threatening or disabling adverse event
- 5 = Death related to adverse event

The definition of Dose-limiting adverse event is determined by the protocol and not by the CTC.

Grading Adverse Events

- Any treatment-related adverse event experienced by a patient is graded using the specific adverse event terms listed in the CTC, v2.0.
- Grading is not modified based on a patient's condition at baseline. Whenever possible, baseline data, including laboratory data and signs and symptoms noted at study entry, should be collected within the institution as course 0, although at present, there is no electronic reporting capability for baseline data within the Clinical Data Update System (CDUS).
- If a given adverse event is experienced more than once during a cycle, only the grade associated with the most severe adverse event is reported.
- Syndromes are graded only when diagnosed by a physician; notes within the CTC, v2.0 provide guidelines to determine when to grade components of each syndrome.
- Adverse events not included in the CTC, v2.0 should be reported and graded under the "Other" adverse event within the appropriate category and graded 1 to 5 according to the general grade definitions provided above.
- Several adverse events contain notes reminding the investigator of other related adverse events that may occur in association and should be considered for grading.
- Multimodality Therapies – Most adverse events and grading criteria are applicable to any treatment modality. Some are specified for a particular modality. The most relevant adverse event should be used to grade adverse events. When it is not possible to determine whether one or both contributed, use the most relevant description of the adverse event.

Scale for Attribution of Adverse Event

Assign attribution of each adverse event reported in an NCI-sponsored IND study using the following criteria:

ATTRIBUTION OF ADVERSE EVENTS		
Code	Descriptor	Definition
5	Definite	The adverse event is <i>clearly related</i> to the investigational agent(s)
4	Probable	The adverse event is <i>likely related</i> to the investigational agent(s)
3	Possible	The adverse event <i>may be related</i> to the investigational agent(s)
2	Unlikely	The adverse event is <i>doubtfully related</i> to the investigational agent(s)
1	Unrelated	The adverse event is <i>clearly not related</i> to the investigational agent(s)

What not to Grade

- Disease progression or signs and symptoms definitely related to disease should not be graded. Objective documentation of progression should always be sought.
- Treatment delivery system malfunctions should not be graded as adverse events.

Options for More Detailed Reporting

When required by the protocol, additional information may be collected using two special modules:

- Adverse Event Module
- Infections Module

Populations and Modalities

When selecting which criteria to use for an adverse event, use the one most consistent with the patient population or treatment modality.

Special criteria for pediatric populations and bone marrow transplant, leukemia, and radiation treatment modalities are shaded in the CTC, v2.0 for easy recognition.

Special Populations

- Pediatrics – Adverse events and adverse event criteria relevant only to children are identified by *italic type* for easy recognition.

Treatment Modalities

- Bone Marrow Transplant Adverse Events – Specialized criteria are included for grading Leukocytes, Platelets, Transfusion: platelets, Transfusion: pRBCs, Weight gain-Veno Occlusive Disease (VOD), Bilirubin-Graft Versus Host

Disease (GVHD), and Stomatitis/pharyngitis for bone marrow transplant, but their use must be designated in the protocol.

- An appendix for grading BMT-related complex/multicomponent events is available in the CTC, v2.0.
- Special grading criteria that may be more pertinent to leukemia, but that require calculations, are available for grading Hemoglobin (Hgb), Neutrophils, Platelets, and Fibrinogen for leukemia studies, but their use must be designated in the protocol.
- Radiation therapy adverse events are subdivided by time of onset.
 - Acute Radiation Effects (day 1 through day 90) are included in the main listing of adverse events.
 - Late Radiation Effects (all effects seen after 90 days from the beginning of radiation therapy are considered late effects) developed by RTOG and EORTC are in Appendix IV of the CTC, v2.0.

Questions and Comments:

If you have any questions or comments regarding the Common Toxicity Criteria, Version 2.0, please contact the NCI CTEP Help Desk by telephone (301) 840-8202, fax (301) 948-2242, or E-mail at ncictephelp@ctep.nci.nih.gov.

Additional information regarding the Common Toxicity Criteria is available on the CTEP Home Page (<http://ctep.info.nih.gov>). Other Common Toxicity Criteria information available from the CTEP Home Page:

- Interactive CTC Application
- Download and print CTC, v2.0
- CTC Index
- CTC Manual
- Generic CTC Data Collection Form
- Instructional CTC Slide Presentation

1. INTRODUCTION

The National Cancer Institute (NCI) Common Toxicity Criteria (CTC) were developed in 1982 for use in adverse drug experience reporting, study adverse event summaries, Investigational New Drug (IND) reports to the Food and Drug Administration (FDA), and publications. The CTC have been used widely for collecting treatment-related adverse event data to facilitate the evaluation of new cancer therapies, treatment modalities, and supportive measures. The original version of the CTC had 49 adverse event terms grouped in 18 categories, each with criteria for grading the severity of the adverse event. In the intervening years, in an effort to report additional adverse events seen in their studies, many groups independently added supplemental adverse event criteria to describe adverse events that were not originally included. Consequently, criteria adopted by various groups differed. To improve completeness, accuracy, and precision of the CTC, and to standardize reporting across groups and therapeutic modalities, a Common Toxicity Criteria Review Committee was assembled to revise and expand the CTC to meet current needs.

1.1 Purpose of this Manual

This manual has been developed to assist users in making the transition from the original CTC to the revised and expanded Cancer Therapy Evaluation Program, Common Toxicity Criteria, Version 2.0 (CTC, v2.0) and to introduce investigators who have never used the CTC to this grading system.

1.2 Making the Entire CTC Available to those Responsible for Grading Adverse Events

To ensure accuracy, the entire CTC, v2.0 should be readily available to those grading adverse events at each site where patients are evaluated. NCI only requires grading of those adverse events that occur (unless a protocol mandates grading of specific terms, even when they do not occur).

1.3 Defining Adverse Event

- **Toxicity** – Toxicity is NOT clearly defined by regulatory organizations. The term toxicity is generally used for an adverse event that is possibly, probably, or definitely related to the agent or treatment.

Note: The Cancer Therapy Evaluation Program CTC, v2.0 continues to use the term “toxicity” for historical reasons, but recommends that the term “adverse event” with its attributes be used instead whenever possible.

- **Adverse Event** – Any unfavorable or unintended symptom, sign, or disease (including an abnormal laboratory finding), temporally associated with the use of a medical treatment or procedure that may or may NOT be considered related to the medical treatment or procedure.

1.4 Specificity of the CTC

The CTC, v2.0 and its associated grading criteria are very specific. Although more individual adverse events are included in the new version, *the number of events a patient experiences will not change*. In the revision process, care was taken to ensure that, wherever possible, each adverse event represented a single clearly definable clinical entity. In most instances, the CTC, v2.0 will provide an adverse event term and grade that more precisely describes the adverse event. The compilation of adverse events used to describe an incident will provide more complete characterization of the events that occur; they do not necessarily indicate more toxic agents. The goal of the CTC, v2.0 is to facilitate a description of the adverse events that do occur. The CTC, v2.0 includes “Also Consider” notes associated with adverse events to direct the user toward other adverse events that require grading if they also occurred.

2. ORGANIZATION OF THE CTC

The CTC, v2.0 includes 24 categories of adverse events with more than 200 individual adverse events. In addition, there are six appendices fully described in Section 2.6.

2.1 Adverse Event Categories in the Revised CTC

The primary organization of the CTC, v2.0 is based on pathophysiological (e.g., Allergy/Immunology) and anatomical (e.g., Dermatology/Skin) categories to facilitate location of related adverse events. The following is a list of categories of adverse events in the CTC, v2.0; new categories or categories with expanded titles are identified by bold type.

Categories in the CTC, v2.0

- ALLERGY/IMMUNOLOGY
- AUDITORY/HEARING
- BLOOD/BONE MARROW
- **CARDIOVASCULAR (ARRHYTHMIA)**
- **CARDIOVASCULAR (GENERAL)**
- COAGULATION
- CONSTITUTIONAL SYMPTOMS
- DERMATOLOGY/SKIN
- ENDOCRINE
- GASTROINTESTINAL
- HEMORRHAGE
- HEPATIC
- INFECTION OR FEBRILE NEUTROPENIA
- LYMPHATICS
- METABOLIC/LABORATORY
- **MUSCULOSKELETAL**
- NEUROLOGY
- **OCULAR/VISUAL**
- PAIN
- PULMONARY
- **RENAL/GENITOURINARY**
- **SECONDARY MALIGNANCIES**
- **SEXUAL/REPRODUCTIVE FUNCTION**
- **SYNDROMES**

Within each of these categories, specific adverse events are listed alphabetically and graded.

2.2 Adverse Event Listings

In revising the CTC, attention was directed to adverse events that occur with varying cancer therapies and patient populations. The CTC, v2.0 classifies adverse events that occur with investigational treatments including chemotherapy, biological therapy, radiation therapy, and surgery. For selected adverse events, different grading criteria are provided together for different patient populations. The adverse event name is the same; only the criteria for grading are changed. All special criteria are identified by shaded text. For pediatrics and radiation therapy, these pertinent criteria should be used routinely.

- For the **pediatric population** special adverse events and grading criteria have been added to account for such child-specific problems as developmental deficits or adjusted laboratory values. Pediatric adverse events or notes referring to pediatric adverse events are identified by *italic type*.
- Adverse events and grading criteria specially developed by RTOG for **radiation therapy** are included.
- Special optional criteria for bone marrow transplant have been added to describe and grade some adverse events. Also optional is the BMT-related Complex/Multicomponent Events Appendix included to facilitate the evaluation of events according to published criteria.

The following adverse events must be specified in the protocol if these alternative criteria proposed by leukemia and bone marrow transplant experts are to be used.

- **Leukemia** – criteria requiring calculations for grading changes in Hemoglobin, Platelets, Neutrophils, and Fibrinogen.
- **Bone marrow transplant** – Leukocytes, Platelets, Transfusion: platelets, Transfusion: pRBCs, Weight gain VOD, Bilirubin-GVHD, and Stomatitis/pharyngitis.
- Appendix for BMT-related Complex/Multicomponent Events.

When selecting which criterion to use, choose the one most consistent with the patient population or treatment modality.

2.3 Grades of Adverse Events

For each adverse event, grades are assigned and defined using a scale from 0 to 5 with 0 representing no adverse event within normal limits and 5 representing death related to an adverse event. Specific criteria for each grade are included for each adverse event.

- 0 = No adverse event or within normal limits
- 1 = Mild adverse event
- 2 = Moderate adverse event
- 3 = Severe and undesirable adverse event
- 4 = Life-threatening or disabling adverse event
- 5 = Death related to adverse event

Grading is based on specific clinical criteria that usually require evaluation by the clinician.

Example: CARDIOVASCULAR Category

An acute myocardial infarction would be graded within the CARDIOVASCULAR (GENERAL) category using the grading for Cardiac-ischemia/infarction.

Adverse Event	Grade			
	1	2	3	4
Cardiac-ischemia/infarction	non-specific T – wave flattening or changes	asymptomatic, ST – and T – wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction

Acute myocardial infarction would be graded as Cardiac-ischemia/infarction, Grade 4.

2.4 Adverse Events Not Included in the CTC, v2.0

Adverse events not included in the CTC, v2.0 should be reported and graded under the “Other” adverse event within the appropriate category and graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening or disabling (Grade 4), or fatal (Grade 5) using the general definitions provided. New adverse events may be submitted to the NCI CTEP Help Desk where the CTC Change Management Committee will compile them for annual evaluation. A subcommittee for the CTC Revision Group will assess new adverse event terms for inclusion in future updates.

2.5 Where to Find Adverse Events from the 1982 Version of the CTC

Many of the adverse events included in the 1982 version of the CTC have been retained in the current version. In many cases, the names of the adverse events have been retained, but the grading criteria have been refined. In other cases, original adverse events have been split into two or more different adverse events. Several examples of these are displayed below:

CTC 1982 Version	CTC, v2.0
Pulmonary	Adult Respiratory Distress Syndrome (ARDS) Carbon monoxide diffusion capacity (DLCO) Cough Dyspnea FEV1 Hypoxia Pneumonitis/infiltrates Pneumothorax Pulmonary fibrosis
Transaminase	SGOT (AST) SGPT (ALT)
Weight gain/loss	Weight gain Weight loss Weight gain - Veno-Occlusive Disease (VOD)

2.6 Highlights of Important Changes

Some specific changes in the CTC, v2.0 include:

- Some adverse events now contain “Also Consider” notes that ask the clinician to consider other adverse events that frequently occur in association. If any are present, they should also be graded.
- In the BLOOD/BONE MARROW category, criteria for the Platelets Grade 4 has changed from $<25,000/\text{mm}^2$ to $<10,000/\text{mm}^2$.
- Cardiovascular adverse events have been divided into two separate categories, CARDIOVASCULAR (ARRHYTHMIA) and CARDIOVASCULAR (GENERAL). Many of the new adverse event terms are very specific and require diagnostic procedures and evaluation by a clinician, e.g., specific arrhythmias are identified from ECG tracings. Only when symptoms suggesting an irregular heartbeat are reported by a patient in the absence of confirmatory ECG diagnostic of a specific arrhythmia, should Palpitations be graded.
- In the CONSTITUTIONAL SYMPTOMS category, Weight gain and Weight loss are included as separate adverse events. When there is an obvious reason for the change in weight such as ascites, edema, pleural effusion, dehydration, vomiting, or diarrhea, also grade the condition causing the weight gain or loss unless it is definitely tumor-related. If no cause is apparent, grade only Weight gain or Weight loss. An additional adverse event, Weight gain-VOD has been added for use in describing weight changes that occur in Veno-Occlusive Disease (VOD) in bone marrow transplant patients.
- There are four important notes at the beginning of the HEMORRHAGE category to provide overall guidance on grading adverse events in this category. New

adverse event terms have been added to differentiate between Hemorrhage/bleeding with Grade 3 or 4 thrombocytopenia and Hemorrhage/bleeding without Grade 3 or 4 thrombocytopenia.

- Adverse Events in the INFECTION/FEBRILE NEUTROPENIA category are categorized as to whether they occurred with or without neutropenia. The adverse event Infection with unknown ANC is available for use in the rare instance when an infection occurs with an unknown neutrophil count. Catheter-related infection is a new, additional adverse event.
- The adverse event terms in the NEUROLOGY category have been extensively revised to provide more specific adverse event descriptions. A number of grading criteria in the original CTC have been split into separate adverse events and graded.
- The PAIN category includes a variety of sites of pain. The intent of this category is to describe pain that may result from (or be exacerbated by) treatment, not pain due to underlying disease alone. One adverse event, Tumor pain is reserved for pain localized to tumor that begins or is exacerbated in relationship to therapy. It is not to be used when there is no change from baseline or when worsening is clearly due to tumor progression.

2.7 Appendices to the CTC

Appendices I to VI are described below:

- **Appendix I:** *Adverse Event Module* for the rare situation when a sponsor or principal investigator requires more detail regarding specific adverse events. This module is required only when mandated by the protocol, generally when a new or previously undescribed adverse event is identified.
- **Appendix II:** *Infection Module* for detailed information regarding infections in the rare situations where additional detail is required. This module is required only when mandated by the protocol.
- **Appendix III:** *Performance Status Scales/Scores.*
- **Appendix IV:** *RTOG/EORTC Late Radiation Morbidity Scoring* includes adverse events that occur more than 90 days after initiation of radiation therapy. These criteria were previously developed by RTOG and EORTC and have not been revised.
- **Appendix V:** *BMT-Specific Adverse Events* for a summary of BMT-Specific Adverse Events that may be used if specified by the protocol. These differ from the standard CTC and may be more relevant to the transplant setting. They are included in the CTC document and listed separately in Appendix V for the convenience of investigators writing transplant protocols.
- **Appendix VI:** *BMT Complex/Multicomponent Events.*

3. HOW TO GRADE ADVERSE EVENTS

3.1 What Not to Grade

- Disease progression or signs and symptoms definitely related to disease should not be graded.

Treatment delivery system malfunctions or sequelae related only to the treatment delivery system, such as a broken needle requiring excision, should not be graded as adverse events.

3.2 Attribution of Causality

To ensure that treatment-related conditions are distinguished from disease-related conditions, attribution of causality is a critical though often difficult first step in grading adverse events. All symptoms, signs, or diseases (including abnormal laboratory findings), that might be associated with investigational agents or therapies must be captured and graded. For each event, the attending physician or clinician in conjunction with the research nurse who examined and evaluated the patient, should assign the attribution. This important task must not be performed by data managers who are removed from the clinical assessment of the patient.

Attribution should be determined using the following criteria:

ATTRIBUTION OF ADVERSE EVENTS		
Code	Descriptor	Definition
5	Definite	The adverse event is <i>clearly related</i> to the investigational agent(s)
4	Probable	The adverse event is <i>likely related</i> to the investigational agent(s)
3	Possible	The adverse event <i>may be related</i> to the investigational agent(s)
2	Unlikely	The adverse event is <i>doubtfully related</i> to the investigational agent(s)
1	Unrelated	The adverse event is <i>clearly not related</i> to the investigational agent(s)

Investigators must document and grade adverse event data if there is any probable, possible or definite relationship to the agent. Adverse events that are definitely related to disease should not be graded. If an adverse event is caused by a combination of treatment and disease, the adverse event should be graded as it is observed with no adjustment. Early in the development of an agent, when little is known of an agent's safety profile, it is especially important to maintain a high level of suspicion and report adverse events that may be agent-related adverse events. Careful reporting is needed to identify idiosyncratic or low frequency agent-related adverse events that may not yet have been identified.

Note that requirements for expedited reporting for serious and unexpected events are specified in each protocol.

3.3 Grading at Baseline

Investigators are encouraged to record baseline values as course 0, though NCI does not currently provide a mechanism for electronic capture of baseline data in the Clinical Data Update System (CDUS). Course 0 baseline pretreatment information will be considered for future updates of the CDUS. No modification in grading should be made to account for abnormalities noted at baseline. For example, if a patient enters a trial with an AST value twice the upper limit of normal (Grade 1) and at the end of cycle two of therapy the AST is 6 times the upper limit of normal, Grade 3 AST should be reported (in this case, course 0 or baseline AST would be Grade 1). Note that the availability of Course 0 information allows subsequent analysis of AST abnormalities according to whether patients had preexisting hepatic abnormalities or not.

3.4 Documenting Related Adverse Events

In some cases an adverse event will be associated with the occurrence of one or more additional adverse events. These may or may not require grading, depending upon the specific case. In general, related adverse events must be graded when the related adverse event is clinically significant and provides relevant information to allow evaluators of the data to more fully characterize an adverse event. If several adverse events are actually due to one primary diagnosis, it is generally not necessary to include all of the components because they are expected. Several examples follow.

Example: GASTROINTESTINAL Category

A patient has diarrhea with dehydration causing hypotension and requiring parenteral support.

- The classification of Diarrhea as Grade 3 requires an increase of ≥ 7 stools per day, or be so severe that parenteral support is required for dehydration.
- If dehydration did occur, it should also be graded. The dehydration may be:
 - Grade 2, requiring IV fluid replacement (brief);
 - Grade 3, requiring IV fluid replacement (sustained); or
 - Grade 4, hypotension requiring intensive care or hemodynamic collapse.

If the resulting dehydration is Grade 4, then hypotension in the **CARDIOVASCULAR (GENERAL)** category also should be graded.

Adverse Event	Grade			
	1	2	3	4
Diarrhea patients without colostomy:	increase of <4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥ 7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse



Common Toxicity Criteria Manual

Grade				
Adverse Event	1	2	3	4
Dehydration	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse

Also consider Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis), Hypotension.



Grade				
Adverse Event	1	2	3	4
Hypotension	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)

Also consider Syncope (fainting).

Notes: Angina or MI is graded as Cardiac-ischemia/infarction in the CARDIOVASCULAR (GENERAL) category.

For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.

Example: HEMORRHAGE Category

A patient with 20,000 platelets has a hemorrhage of the lower GI tract requiring both platelet transfusion and packed red blood cell transfusion. Her hemoglobin is 7.0 g/dL.

The adverse event Hemorrhage/bleeding with Grade 3 or 4 thrombocytopenia requires that the site or type of bleeding be reported as well as Platelets, Hemoglobin, and, if given, Platelet transfusion, and/or pRBC transfusion.

Grade				
Adverse Event	1	2	3	4
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia	mild without transfusion		requiring transfusion	catastrophic bleeding, requiring major non-elective intervention

Also consider Platelets, Hemoglobin, Transfusion: platelets, Transfusion: pRBCs, site or type of bleeding. If the site is not listed, grade as Hemorrhage-Other (Specify site, _____).

Note: This adverse event must be graded for any bleeding with grade 3 or 4 thrombocytopenia.



Grade				
Adverse Event	1	2	3	4
Melena/GI bleeding	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention



Common Toxicity Criteria Manual

Adverse Event	Grade			
	1	2	3	4
Platelets	<LLN - 75.0×10^9 /L <LLN - 75,000/mm ³	≥ 50.0 - $<75.0 \times 10^9$ /L $\geq 50,000$ - $<75,000$ /mm ³	≥ 10.0 - $<50.0 \times 10^9$ /L $\geq 10,000$ - $<50,000$ /mm ³	$<10.0 \times 10^9$ /L $<10,000$ /mm ³
For BMT studies, if specified in the protocol.	≥ 50.0 - $<75.0 \times 10^9$ /L $\geq 50,000$ - $<75,000$ /mm ³	≥ 20.0 - $<50.0 \times 10^9$ /L $\geq 20,000$ - $<50,000$ /mm ³	≥ 10.0 - $<20.0 \times 10^9$ /L $\geq 10,000$ - $<20,000$ /mm ³	$<10.0 \times 10^9$ /L $<10,000$ /mm ³
For leukemia studies or bone marrow infiltrative/myelophthitic process, if specified in the protocol.	10 - $<25\%$ decrease from baseline	25 - $<50\%$ decrease from baseline	50 - $<75\%$ decrease from baseline	$\geq 75\%$ decrease from baseline



Adverse Event	Grade			
	1	2	3	4
Hemoglobin (Hgb)	<LLN - 10.0 g/dL <LLN - 100 g/L <LLN - 6.2 mmol/L	8.0 - <10.0 g/dL 80 - <100 g/L 4.9 - <6.2 mmol/L	6.5 - <8.0 g/dL 65 - <80 g/L 4.0 - <4.9 mmol/L	<6.5 g/dL <65 g/L <4.0 mmol/L
For leukemia studies or bone marrow infiltrative/myelophthitic processes, if specified in the protocol.	10 - $<25\%$ decrease from pretreatment	25 - $<50\%$ decrease from pretreatment	50 - $<75\%$ decrease from pretreatment	$\geq 75\%$ decrease from pretreatment



Adverse Event	Grade			
	1	2	3	4
Transfusion: Platelets	-	-	yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
For BMT studies, if specified in the protocol.	≤ 1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥ 3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding (e.g., HLA or cross matched platelet transfusions).

Also consider Platelets.



Adverse Event	Grade			
	1	2	3	4
Transfusion: pRBCs	-	-	yes	-
For BMT studies, if specified in the protocol.	≤2 u pRBC in 24 hours elective or planned	3 u pRBC in 24 hours elective or planned	≥4 u pRBC in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
For pediatric BMT studies, if specified in the protocol.	≤15mL/kg in 24 hours elective or planned	>15 - ≤30mL/kg in 24 hours elective or planned	>30mL/kg in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin

Also consider Hemoglobin.

Directions for considering additional adverse events are provided as notes in the relevant adverse events. It is important to review the notes in each adverse event to determine if the event mandates further characterization by considering other adverse events and grading them if they occurred.

The following adverse events would be recorded to describe clinical consequences of this patient's thrombocytopenia:

Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia	Grade 3/4
Thrombocytopenia	Grade 3
Melena/GI Bleeding	Grade 3
Platelets	Grade 3
Hemoglobin	Grade 3
Transfusion: Platelets	Grade 3
Transfusion: pRBCs	Grade 3

Example: INFECTION/FEBRILE NEUTROPENIA Category

A patient with Grade 3 neutropenia and a bacterial pneumonia would be graded as follows:

Adverse Event	Grade			
	1	2	3	4
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC <1.0 x 10 ⁹ /L) Also consider Neutrophils.	-	-	present	life-threatening sepsis (e.g., septic shock)

Notes: Hypothermia instead of fever may be associated with neutropenia and is graded here.
In the absence of documented infection grade 3 or 4 neutropenia with fever is graded as Febrile neutropenia.

This event captures the clinically documented infection, in association with neutropenia. The grade of the infection provides information about its seriousness.

Common Toxicity Criteria Manual

Abnormal neutrophil counts must always be graded in neutrophils/granulocytes (ANC/AGC).

The site of infection is not reported unless the Infections Module (Appendix II of the CTC, v2.0) is required by the protocol. Expected symptoms clearly related to the infection, such as cough, hemoptysis, and dyspnea, need not be graded.

Note the following different options to specifically categorize Infection/Febrile Neutropenia plus fever:

Adverse Event	Grade			
	1	2	3	4
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10 ⁹ /L, fever ≥38.5°C) Also consider Neutrophils. Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.	-	-	Present	Life-threatening sepsis (e.g., septic shock)

Adverse Event	Grade			
	1	2	3	4
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC <1.0 x 10 ⁹ /L) Also consider Neutrophils. Notes: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection grade 3 or 4 neutropenia with fever is graded as Febrile neutropenia.	-	-	present	life-threatening sepsis (e.g., septic shock)

Adverse Event	Grade			
	1	2	3	4
Infection with unknown ANC Note: This adverse event criterion is used in the rare case when ANC is unknown.	-	-	present	life-threatening sepsis (e.g., septic shock)

Adverse Event	Grade			
	1	2	3	4
Fever (in the absence of neutropenia, where neutropenia is defined as AGC <1.0 x 10 ⁹ /L) Also consider Allergic reaction/hypersensitivity. Note: The temperature measurements listed above are oral or tympanic.	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	>40.0°C (>104.0°F) for <24hrs	>40.0°C (>104.0°F) for >24hrs

Note the following option for a patient with an infection in the absence of neutropenia:

Adverse Event	Grade			
	1	2	3	4
Infection without neutropenia	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Also consider Neutrophils.				

For patients with neutropenia but no fever or infection, Neutrophils/granulocytes (ANC/AGC) should be graded.

3.5 Grading Adverse Events

Any treatment-related adverse event experienced by a patient is graded using the specific adverse event terms listed in the CTC, v2.0. The nearest match to a grade specified in the CTC, v2.0 is used. As discussed in Section 3.2, grading is not modified based on a patient's condition at baseline.

The clinician is expected to identify and confirm the grade for each adverse event reported.

Report only the most severe grade of a specific adverse event that occurs more than once in a course of therapy.

Several sources of information for adverse event grading may be encountered:

- Patient diary reports of adverse event** - Many investigators require patients to maintain a record of any symptoms or abnormalities they experience during a course of therapy. These diaries most often are discussed when the patient comes in to the clinic for the next treatment. The interviewer grades adverse events reported at each visit.
- History and physical exam** – It has been demonstrated that adverse events will not be identified unless appropriate questions are asked and necessary examinations performed. It is necessary to develop interviewing techniques to elicit important adverse event information from patients. Review of systems should be performed as part of the medical history. When symptoms or signs are elicited, more specific questions will be required. For example, if a patient reports severe diarrhea, medical personnel should ask additional questions to determine whether the patient also had hematochezia (blood in stools), abdominal pain, or thirst (suggesting dehydration), lightheadedness, syncope, or other related adverse events. These queries should be carefully structured using the clinician's knowledge of the physiological relationships among symptoms so that all relevant information can be elicited from the patient. Guidance for developing some of these queries is available in the notes attached to the adverse events in the CTC, v2.0. These notes suggest relevant related adverse events that should be documented and graded if they occurred. The physical examination must also be sufficiently thorough to identify clinical signs suggesting adverse events.
- Clinical emergencies** – Sometimes severe adverse events are encountered. These are usually graded and recorded at the time of the event. When additional

information becomes available later, it must be recorded and grading changes may be necessary.

3.6 Syndromes

Syndromes are graded only when a physician has diagnosed a syndrome. In general, when a syndrome is diagnosed and graded using CTC, v2.0 criteria, relevant laboratory values also are graded. These provide additional documentation of the severity of the syndrome. The notes within the CTC, v2.0 provide guidelines for each syndrome.

The syndromes included in the CTC, v2.0 are:

- Acute vascular leak syndrome
- ARDS (adult respiratory distress syndrome)
- Autoimmune reactions
- DIC (disseminated intravascular coagulation)
- Fanconi's syndrome
- Renal tubular acidosis
- Stevens-Johnson syndrome
- SIADH (syndrome of inappropriate antidiuretic hormone)
- Thrombotic microangiopathy
- Tumor flare
- Tumor lysis syndrome
- Urinary electrolyte wasting

For BMT protocols, complex/multicomponent events can be graded using the BMT-specific grading scales provided in Appendix VI of the CTC, v2.0, if specified in the protocol. Only the adverse events that comprise the event are to be graded. In some cases, additional information about the severity of these events may be required by the protocol. The BMT-related complex/multicomponent events are:

- Failure to engraft
- Graft versus host disease
- Stem cell infusion complications
- Venous Occlusive Disease (VOD)

3.7 Dose-limiting Adverse Event

The definition of Dose-limiting Adverse Event(s) (DLT) is determined by the individual protocol, not the CTC. Although it would be convenient to assume that all Grade 3 adverse events represent dose limiting toxicities, this is not appropriate. Acceptable adverse events vary with the patient population and the anticipated outcome

of the treatment. More severe adverse events may be acceptable with a potentially curative regimen than with a palliative treatment.

4. SUPPLEMENTARY FORMS

Two forms are available for collecting additional information; neither of these forms is required unless specified by the protocol.

4.1 Adverse Event Module

An Adverse Event Module (Appendix I of the CTC, v2.0) is available to collect more detailed information regarding specific adverse events, such as duration of the adverse experience, time to partial or complete recovery, severity over time, and comments on the event. This standardized form is to be used in the rare cases when more detailed reporting is needed to characterize a new or particularly severe adverse event. It may be implemented as part of the original protocol document or as a protocol amendment.

4.2 Infection Module

An Infection Module (Appendix II of the CTC, v2.0) has been developed to provide additional detail to help in evaluation of infections. It allows collection of information about the type of infection, site(s) of infection, and microorganism. Use of this standardized form may be required as part of the original protocol document, or requested through protocol amendment, when more detailed information is pertinent.

5. GRADING TOXICITIES IN SPECIAL POPULATIONS

Special grading criteria have been developed for several situations. They are identified by shading the grading criteria.

5.1 Leukemia Special Adverse Event Criteria

Unlike patients with solid tumors, patients with acute leukemia usually present with evidence of bone marrow compromise (high marrow and blood blast counts, suppression of normal hematopoiesis) with granulocytopenia, thrombocytopenia, and frequently with associated complications, such as fatigue, infections, and bleeding. Successful therapy in acute leukemia often relies on significant suppression of both malignant and normal hematopoiesis.

For this reason, special criteria for some adverse events in the BLOOD/BONE MARROW and COAGULATION categories have been developed at the request of some physicians specializing in the treatment of leukemia and bone marrow myelophthitic processes. These require calculation of change from pretreatment values. These specialized criteria for Hemoglobin (Hgb), Platelets, Neutrophils/granulocytes (ANC/AGC), and Fibrinogen are listed under the adverse event name and labeled for use in leukemia studies, when the protocol so specifies. If the protocol does not include specification for these special criteria, the standard criteria are to be used.

5.2 Bone Marrow/Stem Cell Transplant

In most instances, adverse events encountered in bone marrow transplant are graded using the standard criteria to facilitate comparison of adverse events of treatments with different modalities. However, some specialized criteria for transplants were developed by a group of physicians who specialize in transplants and who requested criteria more appropriate for the transplant setting. These include Leukocytes, Neutrophils/granulocytes, Platelets, Transfusion: platelets, Transfusion: pRBCs, Thrombotic microangiopathy, Weight gain VOD, Rash/dermatitis, Rash/desquamation-GVHD, Diarrhea-GVHD, Stomatitis/pharyngitis and Bilirubin-GVHD. Specialized criteria are necessary because more severe adverse events are anticipated in these patients. These special criteria are included under the name of the adverse event in shaded text labeled for use in transplant protocols. Some physicians also wished to provide guidelines to facilitate evaluation of complex/multicomponent events according to published criteria. These guidelines can be found in Appendix VI of the CTC, v2.0.

Example: BLOOD/BONE MARROW Category

Adverse Event	Grade			
	1	2	3	4
Platelets	<LLN - 75.0×10^9 /L <LLN - 75,000/mm ³	≥ 50.0 - $<75.0 \times 10^9$ /L $\geq 50,000$ - $<75,000$ /mm ³	≥ 10.0 - $<50.0 \times 10^9$ /L $\geq 10,000$ - $<50,000$ /mm ³	$<10.0 \times 10^9$ /L $<10,000$ /mm ³
For BMT studies, if specified in the protocol.	≥ 50.0 - $<75.0 \times 10^9$ /L $\geq 50,000$ - $<75,000$ /mm ³	≥ 20.0 - $<50.0 \times 10^9$ /L $\geq 20,000$ - $<50,000$ /mm ³	≥ 10.0 - $<20.0 \times 10^9$ /L $\geq 10,000$ - $<20,000$ /mm ³	$<10.0 \times 10^9$ /L $<10,000$ /mm ³
For leukemia studies or bone marrow infiltrative/ myelophthisic process, if specified in the protocol.	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	$\geq 75\%$ decrease from baseline

5.3 Pediatric Adverse Event Criteria

Most of the adverse events included in the CTC, v2.0 are appropriate for both adult and pediatric populations; however, some additions or modifications were required to meet specific needs of clinicians treating pediatric patients. In some cases, adverse events that occur only in pediatric populations have been added. In other cases, notes have been added to provide additional definition needed for these adverse events when they occur in the pediatric setting. Several events with criteria specific to pediatric populations on BMT studies have also been added, including, Leukocytes, Lymphopenia, Transfusion: pRBCs and Diarrhea, and can be used only if specified in the protocol. Leukemia-related pediatric adverse events are graded using the same criteria as that listed for adult populations. Pediatric adverse events and notes on pediatric adverse events are identified by *italic type* for easy recognition.

Example: Pediatric-Specific Adverse Event in the NEUROLOGY Category

Adverse Event	Grade			
	1	2	3	4
<i>Cognitive disturbance/ learning problems</i>	<i>cognitive disability; not interfering with work/school performance; preservation of intelligence</i>	<i>cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones</i>	<i>cognitive disability; resulting in significant impairment of work/school performance; cognitive decline > 2 SD</i>	<i>inability to work/frank mental retardation</i>

Example: Pediatric-Specific Criteria in the BLOOD/BONE MARROW Category

Adverse Event	Grade			
	1	2	3	4
Leukocytes (total WBC)	<LLN - 3.0×10^9 /L <LLN - 3000/mm ³	≥ 2.0 - $<3.0 \times 10^9$ /L ≥ 2000 - <3000 /mm ³	≥ 1.0 - $<2.0 \times 10^9$ /L ≥ 1000 - <2000 /mm ³	$<1.0 \times 10^9$ /L <1000 /mm ³
For BMT studies, if specified in the protocol.	≥ 2.0 - $<3.0 \times 10^9$ /L ≥ 2000 - <3000 /mm ³	≥ 1.0 - $<2.0 \times 10^9$ /L ≥ 1000 - <2000 /mm ³	≥ 0.5 - $<1.0 \times 10^9$ /L ≥ 500 - <1000 /mm ³	$<0.5 \times 10^9$ /L <500 /mm ³
<i>For pediatric BMT studies (using age, race and sex normal values), if specified in the protocol.</i>	≥ 75 - $<100\%$ LLN	≥ 50 - $<75\%$ LLN	≥ 25 - 50% LLN	$<25\%$ LLN

6. RADIATION THERAPY TOXICITIES

In reporting adverse events associated with radiation therapy, it is necessary to differentiate between acute and late adverse events. Acute adverse events are defined as those adverse events that occur from day 1, or commencement of radiation therapy, through day 90. All effects seen after 90 days from the beginning of radiation therapy are considered late effects.

6.1 Acute Radiation Adverse Event

Acute adverse events associated with radiation therapy are included in the main body of the CTC, v2.0. Most of these acute adverse event names are identical to those induced by other modalities, although some have special criteria added to aid grading when the adverse event is believed to be associated with radiation therapy. Adverse events with a radiation designation are to be used for radiation therapy only.

The radiation-related adverse events included in the CTC, v2.0 are:

- Radiation dermatitis
- Radiation recall reaction
- Dysphagia-esophageal related to radiation
- Dysphagia-pharyngeal related to radiation
- Mucositis due to radiation
- Pain due to radiation

Example: DERMATOLOGY/SKIN Category

Adverse Event	Grade			
	1	2	3	4
Radiation dermatitis	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation ≥ 1.5 cm diameter and not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Note: Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.				

At the request of radiation oncologists, a separate adverse event, Pain due to radiation, was developed. Pain is not incorporated into the grading criterion for other radiation-related adverse events.

6.2 Late Radiation Effects

Late radiation effects (i.e., effects that first occur 90 days or more after initiation of radiation therapy) are to be graded using a separate scoring system, which is contained in Appendix IV of the CTC, v2.0. These criteria are the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. The Common Toxicity Criteria Review Committee did not revise these criteria.

The RTOG/EORTC Late Radiation Morbidity Scoring Scheme includes scoring criteria for radiation effects to the:

- Bladder
- Bone
- Brain
- Esophagus
- Heart
- Joint
- Kidney
- Larynx
- Liver
- Lung
- Mucous membrane
- Salivary glands
- Skin
- Small/Large intestine
- Spinal cord
- Subcutaneous tissue

- Eye
- Other (Specify)

7. MULTIMODALITY THERAPIES

Most adverse events and grading criteria are applicable to any treatment modality and should be used to classify adverse events regardless of which modality causes the adverse event unless otherwise specified. In the following example, the criteria are identical regardless of modality of therapy. Criteria are the same whether urinary incontinence is associated with cytotoxic chemotherapy, radiation therapy, or surgery.

Example: RENAL/GENITOURINARY Category

Adverse Event	Grade			
	1	2	3	4
Incontinence	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-

7.1 Grading Adverse Events in Multimodality Therapies when Options are Available

It is well documented that acute and chronic radiation adverse events may be exacerbated by the simultaneous administration of some chemotherapy agents with radiation. Some protocols are developed to take advantage of the radiosensitizing nature of some chemotherapy agents.

When an adverse event occurs in a multimodality therapy, it should be graded using the most relevant description of an adverse event whether it is one from the standard list or one that is specifically for radiation therapy. The adverse event should be graded using the grading criterion that most closely matches the clinical situation. It should not be modified to account for the anticipated increased effect. Most often, it is not possible to separate the contribution of the individual modalities, and it is not the purpose of the CTC, v2.0 to do so. The purpose of the CTC, v2.0 is to describe the adverse event.

8. HARMONIZATION WITH THE INTERNATIONAL MEDICAL TERMINOLOGY (IMT)

As part of its commitment to the International Conference on Harmonization, the US FDA agreed to adopt an internationally agreed upon International Medical Terminology (IMT) based on the Medicines Control Agency's Medical Dictionary for Drug Regulatory Reporting (MedDRA) for use in reporting medical information from clinical trials. To facilitate data transfer, NCI has supported the mapping of adverse event names from the CTC, v2.0 to preferred terms in the IMT. The IMT codes are available on the World Wide Web at <http://ctep.info.nih.gov/CtepInformatics/IMT.htm>. This mapping will run in the background of NCI's computerized data systems.

9. CTC USER TOOLS

To facilitate the implementation of the revised CTC, the NCI has developed a CTC site on the World Wide Web located at <http://ctep.info.nih.gov/CTC3/default.htm>. This site provides users a variety of educational tools including the CTC document, the CTC index, and the Generic CTC Data Collection Form. The "Introduction to CTC version 2.0" instructional slide presentation is available as a Microsoft Power Point file and can be requested as an auditory compact disk through the NCI CTEP Help Desk at ncictphelp@ctep.nci.nih.gov. Other tools available from the Web site include:

CTC Interactive Application: Originally designed as a training tool, the interactive CTC application contains an interactive index and links between related toxicities to allow efficient navigation through the CTC categories and adverse events. This interface provides the user the ability to create comma delimited data files from the application's reports option to allow data import to local databases. IMT codes mapped to the adverse events remain in the background of the system but are generated via the report pathway. Providing IMT codes for reports and for downloading into local databases allows another option for sorting and analyzing adverse event data.

Generic CTC Data Collection Form: To assist in the data collection process, the Generic CTC Data Collection Form lists commonly occurring adverse events by category and provides additional space to add other events that may occur in each category. The form can be adapted for individual studies so that expected adverse events can be included depending on the agents administered in the trial.

Instructional CTC Slide Presentation: The "Introduction to the CTC version 2.0" instructional slide presentation provides additional instruction for the CTC and discusses the organization of the CTC, the common principles used to develop it, and instructions for grading adverse events and assigning attribution. It also outlines approaches specific to special populations (e.g., pediatrics).

CTC Training: Representatives from CTEP are currently visiting Cooperative Groups, Cancer Centers and other sites to train data managers and clinicians on the use and principles of the revised CTC and the Interactive CTC Application. The instructional slide presentation described above is a primary tool used during the training sessions. Its publication on the Web along with supplemental training information promotes CTC training from any site at any time.

Computer-Based Training: Development of a computer-based training (CBT) application is currently in progress. This application will provide physicians and nurse practitioners practical guidelines for writing progress notes and documenting proper terms and grades for adverse events.

Pilot Hand Held CTC Tool: A hand held computer is currently in the pilot phase of development and will utilize the CTC Interactive Application documenting CTC data. The device allows grading of adverse events at remote sites is able to up- and download information to personal computers.

Appendix I: REVISION OF THE COMMON TOXICITY CRITERIA

The revision of the CTC was undertaken to address long-standing oncology clinical trial needs for better defined adverse event criteria and is part of a larger initiative of the NCI Cancer Therapy Evaluation Program to upgrade its data collection processes. NCI has been assisted by a Common Toxicity Criteria Review Committee, which includes representatives from NCI, U.S., Canadian, European, and Japanese Cooperative Groups; U.S. and European regulatory agencies, the pharmaceutical industry, and investigators and researchers. The CTC revision effort has been influenced by and is consistent with the recent international drive to harmonize vocabularies and develop data transmission standards to facilitate the global interchange of clinical trial and agent development information.

Deficiencies in the Original CTC

Over the years, users of the CTC have recognized omissions in the list of adverse events and in their descriptive criteria. Thus, CTC users frequently found it necessary to add new adverse events to the list in the original version, resulting in a variety of versions from different groups that created inconsistencies and confusion. Many of the adverse events lacked specific criteria and were graded subjectively as mild, moderate, severe, or life threatening. Because these terms lack objective criteria, different investigators could grade the same adverse event differently reducing the reproducibility of grading and making the overall assessment of a multi-site study or comparison of data across studies difficult. Finally, some of the original adverse events included multiple different adverse events so a reviewer of the data could not ascertain which specific adverse event had occurred. Several of these were of differing clinical severity even though they were included in the same grade.

Purpose of the CTC

The CTC, v2.0 addresses many limitations. It is expected that these criteria in CTC, v2.0 will permit greater accuracy by:

- More accurately defining the adverse event profile of an investigational agent,
- Using well-defined criteria for reproducible grading, and

Revision Methodology

The first step in revising the CTC was to collect and compile the adverse events and criteria used by NCI Adult Cooperative Groups², NCI Pediatric Cooperative Groups³, and

² Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG), Gynecological Oncology Group (GOG), North Central Cancer Treatment Group (NCTG), National Surgical Adjuvant Breast and Bowel Project (NSABP), Radiation Therapy Oncology Group (RTOG), Southwest Oncology Group (SWOG).

³ Children's Cooperative Group (CCG), Intergroup Rhabdomyosarcoma (IR), Pediatric Oncology Group (POG), National Wilms' Tumor Study Group (NWTSG).

other clinical trial groups⁴. All the adverse events included by any group were reviewed and “proposed” criteria were developed from the existing criteria and from additions suggested by CTEP investigators and research nurses. The objective was to increase clarity, consistency, and completeness of the adverse event criteria. This proposal was thoroughly reviewed by NCI’s CTEP, the FDA, the National Cancer Institute of Canada (NCIC), NCI’s Division of Cancer Prevention and Control (DCPC), and other potential users of the CTC, v2.0 or of the data generated through its use. Reviewers had expertise in cancer treatment including chemotherapy, radiation therapy, and biological therapy; surgery; nursing; cancer prevention; and data management. This review generated a number of comments, discussions, and suggestions for changes. The current CTC, v2.0 was developed through many iterations based upon reviewer comments and discussion.

More review and comment occurred after the proposed CTC revision was mapped to the International Medical Terminology (IMT) (refer to Section 8 for additional information). This exercise emphasized the existence in the original CTC of adverse events that actually included groupings of multiple adverse events (e.g., the Neurology toxicities) and also revealed needed terms not yet included in the IMT. As a result of the mapping, several multi-concept CTC adverse events were divided into discrete adverse events. Because the IMT was still undergoing final revisions prior to its presentation to the ICH Steering Committee, the CTC/IMT mapping presented a timely opportunity for NCI to request the addition of important oncology clinical terms, thus improving the IMT for use in global oncology trials. The CTC with the IMT mapping was reviewed by another group convened by the NCI, the IMT Coding Group, which included representatives from NCI Cooperative Groups, Cancer Centers, the pharmaceutical industry, FDA, oncology trial nurses, and data managers.

Participants included physicians, nurses, data managers, and regulatory staff. This review led to further revisions.

Implementation issues were the subject of additional meetings held with NCI Cooperative Groups, Cancer Centers, and U01 Grantees who were represented on a Transition Team. The Transition Team considered such issues as the disposition of large historical databases and implementation during ongoing protocols. The Transition Team recommended a phased implementation of the CTC, v2.0 as new protocols are initiated. NCI implemented CTC, v2.0 for all new protocols submitted to the CTEP after March 1998.

The revised CTC proposal was distributed for review to the Common Toxicity Criteria Review Committee, including representatives from the pharmaceutical industry, FDA, the Committee for Proprietary Medicinal Products, and the major clinical trials groups in the US, Canada, Europe, and Japan. The CTC proposal was evaluated by physicians, nurses, data managers, regulatory staff, and statisticians. These reviewers brought experience in medical oncology, leukemia, prevention, biologics, surgery, pediatrics, and radiotherapy. A revised version was distributed to the Common Toxicity Criteria Review Committee in preparation for a meeting in March 1997.

⁴ National Cancer Institute of Canada, European Organization for Research and Treatment of Cancer, Cancer Research Campaign, NCI CNS Cancer Consortia, and the World Health Organization.

The March 1997 meeting ended with resolution of all but a few issues, and teleconferences were held with representative Review Committee participants who volunteered to continue discussion and resolve issues that were not resolved at the meeting because of lack of time. In addition to a few issues remaining in the main body of the CTC, there were issues specific to pediatrics, bone marrow transplant, and radiation therapy that required resolution. Special committees were established to work through the remaining issues in the specialty areas. Pediatric, BMT, and radiation therapy criteria were incorporated into the CTC, v2.0. The revised CTC proposal was distributed to the committee in late 1997. Subsequently, final details were resolved.

NCI plans to coordinate a committee to review and update the CTC, v2.0 on an annual basis using suggestions for clarifications and proposed new adverse events received from the oncology community. As reports of new adverse events are received, additions to the next version of the CTC will be considered.

COMMON TOXICITY CRITERIA QUICK REFERENCE GUIDE

Remove this guide and place in a convenient location for future reference.

Definition of Adverse Event

Toxicity – Toxicity is NOT clearly defined by regulatory organizations. Toxicity has been described as an adverse event that has an attribution (relationship to investigational agent) of possible, probable or definite. To minimize confusion the NCI would recommend that the term toxicity NOT be utilized.

Note: The Cancer Therapy Evaluation Program Common Toxicity Criteria, Version 2.0 (CTC, v2.0) continues to use the term "toxicity" for historical reasons, but recommends that the term "adverse event" with its attribution be used instead whenever possible.

Adverse Event – Any unfavorable symptom, sign, or disease (including an abnormal laboratory finding) temporally associated with the use of a medical treatment or procedure that may or may NOT be considered related to the medical treatment or procedure.

Common Toxicity Criteria (CTC)* – The CTC, v2.0 provides descriptive terminology for adverse event reporting. A grading (severity) scale is provided for each adverse event term.

Common Toxicity Criteria (CTC) Categories

- CTC, v2.0 contains 24 categories.
- CTC, v2.0 is organized by pathophysiology and anatomy.
- Alphabetical listings of adverse event names are placed within categories.
- The entire CTC, v2.0 should always be available for grading adverse events; however, NCI only requires grading of adverse events that occur.

Changes in the CTC, v2.0

Major modifications to the CTC, v2.0 are outlined in Sections 2.4 and 2.5 of the CTC Manual.

Grades (General Definitions)

- 0 = No adverse event or within normal limits
- 1 = Mild adverse event
- 2 = Moderate adverse event
- 3 = Severe and undesirable adverse event
- 4 = Life-threatening or disabling adverse event
- 5 = Death related to adverse event

The definition of a dose-limiting adverse event is determined by the protocol and not by the CTC.

Grading Adverse Events

- Any treatment-related adverse event experienced by a patient is graded using the specific adverse event terms listed in the CTC, v2.0.
- Grading is not modified based on a patient's condition at baseline. Whenever possible, baseline data, including laboratory data and signs and symptoms noted at study entry, should be collected within the institution as course 0, although at present, there is no electronic reporting capability for baseline data within the Clinical Data Update System (CDUS).
- If a given adverse event is experienced on more than one occasion during a cycle, only the grade associated with the most severe adverse event is reported.
- Syndromes are graded only when diagnosed by a physician; notes within the CTC, v2.0 provide guidelines to determine when to grade components of each syndrome.
- Adverse events not included in the CTC, v2.0 should be reported and graded under the "Other" adverse event within the appropriate category and graded 1 to 5 according to the general grade definitions provided above.
- Several adverse events contain notes reminding the investigator of other related adverse events that may occur in association and should be considered for grading.
- Multimodality Therapies – Most adverse events and grading criteria are applicable to any treatment modality. Some are specified for a particular modality. The most relevant adverse event should be used to grade adverse events. When it is not possible to determine whether one or both contributed, use the most relevant description of the adverse event.

* All studies reviewed and approved after March 5, 1998 must utilize the CTC version 2.0 standards 1998 for adverse event grading and attribution.

Scale for Attribution of Adverse Event

Assign attribution of each adverse event reported in an NCI-sponsored IND study using the following criteria:

Attribution of Adverse Events		
Code	Descriptor	Definition
5	Definite	The adverse event is <i>clearly related</i> to the investigational agent(s)
4	Probable	The adverse event is <i>likely related</i> to the investigational agent(s)
3	Possible	The adverse event <i>may be related</i> to the investigational agent(s)
2	Unlikely	The adverse event is <i>doubtfully related</i> to the investigational agent(s)
1	Unrelated	The adverse event is <i>clearly not related</i> to the investigational agent(s)

What not to Grade

- Disease progression or signs and symptoms definitely related to disease should not be graded. Objective documentation of progression should always be sought.
- Treatment delivery system malfunctions should not be graded as adverse events.

Options for More Detailed Reporting

When required by the protocol, additional information may be collected using two special modules:

- Adverse Event Module
- Infections Module

Populations and Modalities

When selecting the criteria to use for an adverse event, use the one most consistent with the patient population or treatment modality.

Special criteria for pediatric populations and bone marrow transplant, leukemia, and radiation treatment modalities are shaded in the CTC, v2.0 for easy recognition.

Special Populations

Pediatrics – Adverse events or adverse event criteria relevant only to children are identified by *italic type* for easy recognition.

Treatment Modalities

- Bone Marrow Transplant Adverse Event – Specialized criteria are included for grading Leukocytes, Platelets, Transfusion: platelets, Transfusion: pRBCs, Weight gain-Veno Occlusive Disease (VOD), Bilirubin-Graft Versus Host Disease (GVHD), and Stomatitis/pharyngitis for bone marrow, but their use must be designated in the protocol.
- An appendix for grading BMT-related complex/multicomponent events is available in the CTC, v2.0.
- Special grading criteria that may be more pertinent to leukemia, but that require calculations, are available for grading Hemoglobin (Hgb), Neutrophils, Platelets, and Fibrinogen for leukemia studies, but their use must be designated in the protocol.
- Radiation therapy adverse events are subdivided by time of onset.
 - Acute Radiation Effects (day 1 through day 90) are included in the main listing of adverse events.
 - Late Radiation Effects (all effects seen after 90 days from the beginning of radiation therapy are considered late effects) developed by RTOG and EORTC are in Appendix IV of the CTC, v2.0.

Questions and Comments

If you have any questions or comments regarding the Common Toxicity Criteria, Version 2.0, please contact the NCI CTEP Help Desk by telephone (301) 840-8202, fax (301) 948-2242, or E-mail at ncictephelp@ctep.nci.nih.gov.

Additional information regarding the Common Toxicity Criteria is available on the CTEP Home Page (<http://ctep.info.nih.gov>). Other Common Toxicity Criteria information available from the CTEP Home Page:

- Interactive CTC Application
- Download and print CTC, v2.0
- CTC Index
- CTC Manual
- Generic CTC Data Collection Form
- Instructional CTC Slide Presentation